

SEQUENCE LISTING

<110> Merck & Co., Inc.
Istituto di Ricerche di Biologia Molecolare P. Angeletti S.p.A.

<120> HCV REPLICONS CONTAINING NS5B FROM
GENOTYPE 2B

<130> 21564Y PCT

<150> 60/517,605
<151> 2003-11-05

<160> 28

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 591
<212> PRT
<213> Artificial Sequence

<220>
<223> modified NS5B

<221> VARIANT
<222> (5)...(5)
<223> Xaa = threonine or serine

<221> VARIANT
<222> (24)...(24)
<223> Xaa = asparagine or serine

<221> VARIANT
<222> (31)...(31)
<223> Xaa = methionine or isoleucine

<221> VARIANT
<222> (376)...(376)
<223> Xaa = isoleucine or leucine

<400> 1
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20 25 30
Phe His Asn Lys Val Tyr Ser Thr Thr Ser Arg Ser Ala Ser Leu Arg
35 40 45
Ala Lys Lys Val Thr Phe Asp Arg Val Gln Val Leu Asp Ala His Tyr
50 55 60
Asp Ser Val Leu Gln Asp Val Lys Arg Ala Ala Ser Lys Val Ser Ala
65 70 75 80
Arg Leu Leu Thr Val Glu Glu Ala Cys Ala Leu Thr Pro Pro His Ser
85 90 95

Ala	Lys	Ser	Arg	Tyr	Gly	Phe	Gly	Ala	Lys	Glu	Val	Arg	Ser	Leu	Ser	100	105	110
Arg	Arg	Ala	Val	Asn	His	Ile	Arg	Ser	Val	Trp	Glu	Asp	Leu	Leu	Glu	115	120	125
Asp	Gln	His	Thr	Pro	Ile	Asp	Thr	Thr	Ile	Met	Ala	Lys	Asn	Glu	Val	130	135	140
Phe	Cys	Ile	Asp	Pro	Thr	Lys	Gly	Gly	Lys	Lys	Pro	Ala	Arg	Leu	Ile	145	150	155
Val	Tyr	Pro	Asp	Leu	Gly	Val	Arg	Val	Cys	Glu	Lys	Met	Ala	Leu	Tyr	165	170	175
Asp	Ile	Ala	Gln	Lys	Leu	Pro	Lys	Ala	Ile	Met	Gly	Pro	Ser	Tyr	Gly	180	185	190
Phe	Gln	Tyr	Ser	Pro	Ala	Glu	Arg	Val	Asp	Phe	Leu	Leu	Lys	Ala	Trp	195	200	205
Gly	Ser	Lys	Lys	Asp	Pro	Met	Gly	Phe	Ser	Tyr	Asp	Thr	Arg	Cys	Phe	210	215	220
Asp	Ser	Thr	Val	Thr	Glu	Arg	Asp	Ile	Arg	Thr	Glu	Glu	Ser	Ile	Tyr	225	230	235
Gln	Ala	Cys	Ser	Leu	Pro	Gln	Glu	Ala	Arg	Thr	Val	Ile	His	Ser	Leu	245	250	255
Thr	Glu	Arg	Leu	Tyr	Val	Gly	Gly	Pro	Met	Thr	Asn	Ser	Lys	Gly	Gln	260	265	270
Ser	Cys	Gly	Tyr	Arg	Arg	Cys	Arg	Ala	Ser	Gly	Val	Phe	Thr	Thr	Ser	275	280	285
Met	Gly	Asn	Thr	Met	Thr	Cys	Tyr	Ile	Lys	Ala	Leu	Ala	Ala	Cys	Lys	290	295	300
Ala	Ala	Gly	Ile	Val	Asp	Pro	Val	Met	Leu	Val	Cys	Gly	Asp	Asp	Leu	305	310	315
Val	Val	Ile	Ser	Glu	Ser	Gln	Gly	Asn	Glu	Asp	Glu	Arg	Asn	Leu		325	330	335
Arg	Ala	Phe	Thr	Glu	Ala	Met	Thr	Arg	Tyr	Ser	Ala	Pro	Pro	Gly	Asp	340	345	350
Leu	Pro	Arg	Pro	Glu	Tyr	Asp	Leu	Glu	Leu	Ile	Thr	Ser	Cys	Ser	Ser	355	360	365
Asn	Val	Ser	Val	Ala	Leu	Asp	Ser	Arg	Gly	Arg	Arg	Arg	Tyr	Phe	Leu	370	375	380
Thr	Arg	Asp	Pro	Thr	Thr	Pro	Xaa	Thr	Arg	Ala	Ala	Trp	Glu	Thr	Val	385	390	395
Arg	His	Ser	Pro	Val	Asn	Ser	Trp	Leu	Gly	Asn	Ile	Ile	Gln	Tyr	Ala	405	410	415
Pro	Thr	Ile	Trp	Val	Arg	Met	Val	Ile	Met	Thr	His	Phe	Phe	Ser	Ile	420	425	430
Leu	Leu	Ala	Gln	Asp	Thr	Leu	Asn	Gln	Asn	Leu	Asn	Phe	Glu	Met	Tyr	435	440	445
Gly	Ala	Val	Tyr	Ser	Val	Asn	Pro	Leu	Asp	Leu	Pro	Ala	Ile	Ile	Glu	450	455	460
Arg	Leu	His	Gly	Leu	Glu	Ala	Phe	Ser	Leu	His	Thr	Tyr	Ser	Pro	His	465	470	475
Glu	Leu	Ser	Arg	Val	Ala	Ala	Thr	Leu	Arg	Lys	Leu	Gly	Ala	Pro	Pro	485	490	495
Leu	Arg	Ala	Trp	Lys	Ser	Arg	Ala	Arg	Ala	Val	Arg	Ala	Ser	Leu	Ile	500	505	510
Ala	Gln	Gly	Ala	Arg	Ala	Ala	Ile	Cys	Gly	Arg	Tyr	Leu	Phe	Asn	Trp	515	520	525

Ala	Val	Lys	Thr	Lys	Leu	Lys	Leu	Thr	Pro	Leu	Pro	Glu	Ala	Ser	Arg
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Leu	Asp	Leu	Ser	Gly	Trp	Phe	Thr	Val	Gly	Ala	Gly	Gly	Gly	Asp	Ile
545					550					555					560
Tyr	His	Ser	Val	Ser	His	Ala	Arg	Pro	Arg	Leu	Leu	Leu	Leu	Cys	Leu
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Leu	Leu	Leu	Ser	Val	Gly	Val	Gly	Ile	Phe	Leu	Leu	Pro	Asp	Arg	
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<210> 2
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 <212> DNA
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<220>
 <223> modified NS5B

<221> variation
 <222> (3)...(3)
 <223> n = A or T

<221> variation
 <222> (9)...(9)
 <223> n = C or A

<221> variation
 <222> (13)...(13)
 <223> n = A or T

<221> variation
 <222> (15)...(15)
 <223> n = A or C

<221> variation
 <222> (21)...(21)
 <223> n = A or G

<221> variation
 <222> (24)...(24)
 <223> n = C or G

<221> variation
 <222> (28)...(28)
 <223> n = T or C

<221> modified_base
 <222> (30)...(30)
 <223> n = G or C

<221> variation
 <222> (33)...(33)
 <223> n = C or A

<221> variation
 <222> (71)...(71)

<223> n = A or G

<221> variation

<222> (83)...(83)

<223> n = G or T

<221> variation

<222> (1174)...(1174)

<223> n = A or C

<400> 2

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<210> 3

<211> 1394

<212> PRT

<213> Artificial Sequence

<220>

<223> modified NS3-5A

<221> VARIANT

<222> (1215)...(1215)

<223> Xaa = asparagine or serine

<221> VARIANT

<222> (904)...(904)

<223> Xaa = valine or alanine

<400> 3

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Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr Cys
      35          40          45
Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr
      50          55          60
Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp
65          70          75          80
Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr
      85          90          95
Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala
      100          105          110
Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu
      115          120          125
Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu
      130          135          140
Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys
145          150          155          160
Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met
      165          170          175
Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro
      180          185          190
Ala Val Pro Gln Thr Phe Gln Val Ala His Leu His Ala Pro Thr Gly
      195          200          205
Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly Tyr
      210          215          220
Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly
225          230          235          240
Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly
      245          250          255
Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr Tyr Gly
      260          265          270
Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile
      275          280          285
Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu Gly Ile
      290          295          300
Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val
305          310          315          320
Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn
      325          330          335
Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe Tyr Gly
      340          345          350
Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu Ile Phe
      355          360          365
Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Ser Gly
      370          375          380
Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val
385          390          395          400

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Ile	Pro	Thr	Ile	Gly	Asp	Val	Val	Val	Val	Ala	Thr	Asp	Ala	Leu	Met	405	410	415
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Val	Thr	Gln	Thr	Val	Asp	Phe	Ser	Leu	Asp	Pro	Thr	Phe	Thr	Ile	Glu	435	440	445
Thr	Thr	Thr	Val	Pro	Gln	Asp	Ala	Val	Ser	Arg	Ser	Gln	Arg	Arg	Gly	450	455	460
Arg	Thr	Gly	Arg	Gly	Arg	Met	Gly	Ile	Tyr	Arg	Phe	Val	Thr	Pro	Gly	465	470	475
Glu	Arg	Pro	Ser	Gly	Met	Phe	Asp	Ser	Ser	Val	Leu	Cys	Glu	Cys	Tyr	485	490	495
Asp	Ala	Gly	Cys	Ala	Trp	Tyr	Glu	Leu	Thr	Pro	Ala	Glu	Thr	Ser	Val	500	505	510
Arg	Leu	Arg	Ala	Tyr	Leu	Asn	Thr	Pro	Gly	Leu	Pro	Val	Cys	Gln	Asp	515	520	525
His	Leu	Glu	Phe	Trp	Glu	Ser	Val	Phe	Thr	Gly	Leu	Thr	His	Ile	Asp	530	535	540
Ala	His	Phe	Leu	Ser	Gln	Thr	Lys	Gln	Ala	Gly	Asp	Asn	Phe	Pro	Tyr	545	550	555
Leu	Val	Ala	Tyr	Gln	Ala	Thr	Val	Cys	Ala	Arg	Ala	Gln	Ala	Pro	Pro	565	570	575
Pro	Ser	Trp	Asp	Gln	Met	Trp	Lys	Cys	Leu	Ile	Arg	Leu	Lys	Pro	Thr	580	585	590
Leu	His	Gly	Pro	Thr	Pro	Leu	Leu	Tyr	Arg	Leu	Gly	Ala	Val	Gln	Asn	595	600	605
Glu	Val	Thr	Leu	Thr	His	Pro	Ile	Thr	Lys	Tyr	Ile	Met	Ala	Cys	Met	610	615	620
Ser	Ala	Asp	Leu	Glu	Val	Val	Thr	Ser	Thr	Trp	Val	Leu	Val	Gly	Gly	625	630	635
Val	Leu	Ala	Ala	Leu	Ala	Ala	Tyr	Cys	Leu	Thr	Thr	Gly	Ser	Val	Val	645	650	655
Ile	Val	Gly	Arg	Ile	Ile	Leu	Ser	Gly	Arg	Pro	Ala	Ile	Val	Pro	Asp	660	665	670
Arg	Glu	Phe	Leu	Tyr	Gln	Glu	Phe	Asp	Glu	Met	Glu	Glu	Cys	Ala	Ser	675	680	685
His	Leu	Pro	Tyr	Ile	Glu	Gln	Gly	Met	Gln	Leu	Ala	Glu	Gln	Phe	Lys	690	695	700
Gln	Lys	Ala	Leu	Gly	Leu	Leu	Gln	Thr	Ala	Thr	Lys	Gln	Ala	Glu	Ala	705	710	715
Ala	Ala	Pro	Val	Val	Glu	Ser	Lys	Trp	Arg	Ala	Leu	Glu	Thr	Phe	Trp	725	730	735
Ala	Lys	His	Met	Trp	Asn	Phe	Ile	Ser	Gly	Ile	Gln	Tyr	Leu	Ala	Gly	740	745	750
Leu	Ser	Thr	Leu	Pro	Gly	Asn	Pro	Ala	Ile	Ala	Ser	Leu	Met	Ala	Phe	755	760	765
Thr	Ala	Ser	Ile	Thr	Ser	Pro	Leu	Thr	Thr	Gln	Ser	Thr	Leu	Leu	Phe	770	775	780
Asn	Ile	Leu	Gly	Gly	Trp	Val	Ala	Ala	Gln	Leu	Ala	Pro	Pro	Ser	Ala	785	790	795
Ala	Ser	Ala	Phe	Val	Gly	Ala	Gly	Ile	Ala	Gly	Ala	Ala	Val	Gly	Ser	805	810	815
Ile	Gly	Leu	Gly	Lys	Val	Leu	Val	Asp	Ile	Leu	Ala	Gly	Tyr	Gly	Ala	820	825	830

Gly Val Ala Gly Ala Leu Val Ala Phe Lys Val Met Ser Gly Glu Met
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 Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro
 850 855 860
 Gly Ala Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His
 865 870 875 880
 Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala
 885 890 895
 Phe Ala Ser Arg Gly Asn His Xaa Ser Pro Thr His Tyr Val Pro Glu
 900 905 910
 Ser Asp Ala Ala Ala Arg Val Thr Gln Ile Leu Ser Ser Leu Thr Ile
 915 920 925
 Thr Gln Leu Leu Lys Arg Leu His Gln Trp Ile Asn Glu Asp Cys Ser
 930 935 940
 Thr Pro Cys Ser Gly Ser Trp Leu Arg Asp Val Trp Asp Trp Ile Cys
 945 950 955 960
 Thr Val Leu Thr Asp Phe Lys Thr Trp Leu Gln Ser Lys Leu Leu Pro
 965 970 975
 Gln Leu Pro Gly Val Pro Phe Phe Ser Cys Gln Arg Gly Tyr Lys Gly
 980 985 990
 Val Trp Arg Gly Asp Gly Ile Met Gln Thr Thr Cys Pro Cys Gly Ala
 995 1000 1005
 Gln Ile Thr Gly His Val Lys Asn Gly Ser Met Arg Ile Val Gly Pro
 1010 1015 1020
 Lys Thr Cys Ser Asn Thr Trp His Gly Thr Phe Pro Ile Asn Ala Tyr
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 Thr Thr Gly Pro Cys Thr Pro Ser Pro Ala Pro Asn Tyr Ser Arg Ala
 1045 1050 1055
 Leu Trp Arg Val Ala Ala Glu Glu Tyr Val Glu Val Thr Arg Val Gly
 1060 1065 1070
 Asp Phe His Tyr Val Thr Gly Met Thr Thr Asp Asn Val Lys Cys Pro
 1075 1080 1085
 Cys Gln Val Pro Ala Pro Glu Phe Phe Thr Glu Val Asp Gly Val Arg
 1090 1095 1100
 Leu His Arg Tyr Ala Pro Ala Cys Arg Pro Leu Leu Arg Glu Glu Val
 1105 1110 1115 1120
 Thr Phe Gln Val Gly Leu Asn Gln Tyr Leu Val Gly Ser Gln Leu Pro
 1125 1130 1135
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 Pro Ser His Ile Thr Ala Glu Thr Ala Lys Arg Arg Leu Ala Arg Gly
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 Ser Pro Pro Ser Leu Ala Ser Ser Ser Ala Ile Gln Leu Ser Ala Pro
 1170 1175 1180
 Ser Leu Lys Ala Thr Cys Thr Thr His His Val Ser Pro Asp Ala Asp
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 Leu Ile Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Xaa Ile
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 Thr Arg Val Glu Ser Glu Asn Lys Val Val Val Leu Asp Ser Phe Asp
 1220 1225 1230
 Pro Leu Arg Ala Glu Glu Asp Glu Arg Glu Val Ser Val Pro Ala Glu
 1235 1240 1245
 Ile Leu Arg Lys Ser Lys Lys Phe Pro Ala Ala Met Pro Ile Trp Ala
 1250 1255 1260

Arg Pro Asp Tyr Asn Pro Pro Leu Leu Glu Ser Trp Lys Asp Pro Asp
 1265 1270 1275 1280
 Tyr Val Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Ile Lys Ala
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 Pro Pro Ile Pro Pro Pro Arg Arg Lys Arg Thr Val Val Leu Thr Glu
 1300 1305 1310
 Ser Ser Val Ser Ser Ala Leu Ala Glu Leu Ala Thr Lys Thr Phe Gly
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 Ser Ser Glu Ser Ser Ala Val Asp Ser Gly Thr Ala Thr Ala Leu Pro
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 Asp Gln Ala Ser Asp Asp Gly Asp Lys Gly Ser Asp Val Glu Ser Tyr
 1345 1350 1355 1360
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<210> 4
 <211> 4182
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> modified NS3-5A

<221> variation
 <222> (2711)...(2711)
 <223> n = T or C

<221> variation
 <222> (3645)...(3645)
 <223> n = A or G

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Gln Asp Ile Gln Pro Ala Ile Gln Ser Ser Trp Pro Lys Leu Glu Gln
 35          40          45
Phe Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu
 50          55          60
Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Val Ala Ser Met Met
 65          70          75          80
Ala Phe Ser Ala Ala Leu Thr Ser Pro Leu Pro Thr Ser Thr Thr Ile
 85          90          95
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		115						120					125		
Gly	Ser	Ile	Gly	Leu	Gly	Lys	Ile	Leu	Val	Asp	Val	Leu	Ala	Gly	Tyr
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Gly	Ala	Gly	Ile	Ser	Gly	Ala	Leu	Val	Ala	Phe	Lys	Ile	Met	Ser	Gly
145					150					155					160
Glu	Lys	Pro	Thr	Val	Glu	Asp	Val	Val	Asn	Leu	Leu	Pro	Ala	Ile	Leu
				165					170						175
Ser	Pro	Gly	Ala	Leu	Val	Val	Gly	Val	Ile	Cys	Ala	Ala	Ile	Leu	Arg
			180					185							190
Arg	His	Val	Gly	Pro	Gly	Glu	Gly	Ala	Val	Gln	Trp	Met	Asn	Arg	Leu
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225					230					235					240
Thr	Ile	Thr	Gln	Leu	Leu	Lys	Arg	Leu	His	Gln	Trp	Ile	Asn	Glu	Asp
			245						250						255
Cys	Ser	Thr	Pro	Cys											
			260												